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L3 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
AN 2004362217 MEDLINE
DN PubMed ID: 15087430
TI Pregnancy-associated plasma protein-a production in rat granulosa cells:
stimulation by follicle-stimulating hormone and inhibition by the oocyte-derived bone morphogenetic protein-15.
AU Matsui Motozumi; Sonntag Barbara; Hwang Seong Soo; Byerly Tara; Hourvitz
Ariel; Adashi Eli Y; Shimasaki Shunichi; Erickson Gregory F
CS Department of Reproductive Medicine, University of California San Diego,
La Jolla, California 92093-0674, USA.
NC U54 HD12303 (NICHD)
SO Endocrinology, (2004 Aug) 145 (8) 3686-95. Electronic Publication:
2004-04-15.
Journal code: 0375040. ISSN: 0013-7227.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200408
ED Entered STN: 20040722
Last Updated on STN: 20040818
Entered Medline: 20040817
AB Pregnancy-associated plasma protein-A (PAPP-A) is the major IGF binding
protein-4 (IGFBP-4) protease in follicular fluid, consistent with its
proposed role in folliculogenesis. Despite growing interest, almost
nothing is known about how PAPP-A expression is regulated in any tissue.
Here we show that FSH and oocytes regulate PAPP-A expression in granulosa
cells (GCs). By in situ hybridization, ovary PAPP-A mRNA was markedly
increased by pregnant mare serum gonadotropin treatment, and the message
was localized to the membrana GCs but not cumulus GCs (CGCs) of dominant
follicles. To explore the mechanism, we used primary cultures of rat GCs.
Control (untreated) cells produced little or no PAPP-A spontaneously.
Conversely, FSH markedly stimulated PAPP-A mRNA and protein in a dose- and
time-dependent fashion. Interestingly, PAPP-A expression in isolated CGCs
was also strongly induced by FSH, and the induction was inhibited by added

oocytes. To investigate the nature of the inhibition, we tested the effect of oocyte-derived bone morphogenetic protein-15 (BMP-15). BMP-15 alone had no effect on basal levels of PAPP-A expression by cultures of membrana GCs or CGCs. However, BMP-15 markedly inhibited the FSH stimulation of PAPP-A production in a dose-dependent manner. The cleavage of IGFBP-4 by conditioned media from FSH-treated GCs was completely inhibited by anti-PAPP-A **antibody**, indicating the **IGFBP -4 protease** secreted by GCs is PAPP-A. These results demonstrate stimulatory and inhibitory roles for FSH and BMP-15, respectively, in regulating PAPP-A production by GCs. We propose that FSH and oocyte-derived BMP-15 form a controlling network that ensures the spatiotemporal pattern of GC PAPP-A expression in the dominant follicle.

L3 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 2
AN 2002654650 MEDLINE
DN PubMed ID: 12414897
TI Pregnancy-associated plasma protein A proteolytic activity is associated with the human placental trophoblast cell membrane.
AU Sun Irene Y C; Overgaard Michael T; Oxvig Claus; Giudice Linda C
CS Department of Gynecology and Obstetrics, Center for Research on Women's Health and Reproductive Medicine, Stanford University Medical Center, Stanford, CA 94305-5317, USA.
NC HD 35789-05 (NICHD)
SO Journal of clinical endocrinology and metabolism, (2002 Nov) 87 (11) 5235-40.
Journal code: 0375362. ISSN: 0021-972X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200212
ED Entered STN: 20021105
Last Updated on STN: 20021217
Entered Medline: 20021209
AB Pregnancy-associated plasma protein-A (PAPP-A) is a product of the placenta and decidua and is secreted into the maternal circulation during human pregnancy. It recently has been identified as an IGF binding

protein (IGFBP)-4 protease. Presumed functions at the maternal-fetal interface are to proteolyze IGFBP-4 and thus increase IGF bioavailability locally in the placenta, to promote IGF-II-mediated trophoblast invasion into the maternal decidua, and to modulate IGF regulation of steroidogenesis and glucose and amino acid transport in the villous.

Herein, we have investigated the possibility that IGFBP-4 proteolysis may occur on the trophoblast cell membrane, presumably to increase local bioavailable IGF for interactions with cognate IGF membrane receptors.

Human trophoblasts were cultured, trophoblast plasma membranes were isolated and solubilized, and IGFBP-4 protease activity and PAPP-A immunoreactivity in the solubilized plasma membrane fraction were investigated. IGFBP-4 protease activity was detected in solubilized human trophoblast membranes, resulting in cleavage of recombinant human IGFBP-4 into 18- and 14-kDa fragments, detected by Western immunoblot analysis.

This protease activity was dependent on the presence of IGF-II, and its metal ion dependence was demonstrated by inhibition of the protease by the metal chelators, EDTA and EGTA. The presence of PAPP-A in solubilized human trophoblast membranes was demonstrated by Western immunoblotting.

Trophoblast membrane PAPP-A had a relative molecular weight of approximately 200 kDa and comigrated on (reducing) SDS-PAGE with recombinant human PAPP-A and PAPP-A secreted into media conditioned by cultured human trophoblasts. IGFBP-4 protease activity was not detected after immunodepletion of PAPP-A from the trophoblast membrane fraction with PAPP-A **polyclonal antibodies**, suggesting the identity of the membrane-derived **IGFBP-4 protease** as PAPP-A. Immunocytochemistry revealed PAPP-A on the cell membrane and in the cytoplasm of human trophoblasts in culture.

Together, these data demonstrate the presence of an IGF-II- and metal-dependent IGFBP-4 protease activity in human trophoblast plasma membranes, identified as PAPP-A, which is well situated to proteolyze

IGFBP-4 at the maternal-placental interface to facilitate IGF action at the villous surface and/or the invading extravillous cytotrophoblast.

L3 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 3
AN 2002255160 MEDLINE
DN PubMed ID: 11994388
TI Identification and regulation of the IGFBP-4 protease and its physiological inhibitor in human trophoblasts and endometrial stroma: evidence for paracrine regulation of IGF-II bioavailability in the placental bed during human implantation.
AU Giudice L C; Conover C A; Bale L; Faessen G H; Ilg K; Sun I; Imani B; Suen L-F; Irwin J C; Christiansen M; Overgaard M T; Oxvig C
CS Department of Gynecology and Obstetrics, Stanford University Medical Center, Stanford, California 94305, USA.. giudice@stanford.edu
NC U54 HD31398 (NICHD)
SO Journal of clinical endocrinology and metabolism, (2002 May) 87 (5) 2359-66.
Journal code: 0375362. ISSN: 0021-972X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200206
ED Entered STN: 20020508
Last Updated on STN: 20020615
Entered Medline: 20020614
AB The IGF family plays an important role in implantation and placental physiology. IGF-II is abundantly expressed by placental trophoblasts, and IGF binding protein (IGFBP)-4, a potent inhibitor of IGF actions, is the second most abundant IGFBP in the placental bed, expressed exclusively by the maternal decidua. Proteolysis of IGFBP-4 results in decreased affinity for IGF peptides, thereby enhancing IGF actions. In the current study, we have identified the IGFBP-4 protease and its inhibitor in human trophoblast and decidualized endometrial stromal cell cultures, and we have investigated their regulation in an effort to understand control of IGF-II bioavailability at the placental-decidual interface in human

implantation. IGFBP-4 protease activity was detected in conditioned media (CM) from human trophoblasts and decidualized endometrial stromal cells using (125)I-IGFBP-4 substrate. Identification of the IGFBP-4 protease as pregnancy-associated plasma protein-A (PAPP-A) was confirmed by specific immunoinhibition and immunodepletion of the **IGFBP-4 protease** activity with specific PAPP-A **antibodies**. The IGFBP-4 protease activity was IGF-II-dependent in trophoblast CM. In decidualized stromal CM, PAPP-A/IGFBP-4 protease activity was also IGF-II-dependent, but was evident only when IGF-II was added in molar excess of the predominant IGFBP in decidualized stromal cell CM, IGFBP-1, supporting bioavailable IGF-II as a key cofactor of IGFBP-4 proteolysis by PAPP-A. Cultured first and second trimester human trophoblasts (n = 5) secreted PAPP-A into CM with mean +/- SEM levels of 172.4 +/- 32.8 mIU/liter.10(5) cells, determined by specific ELISA. PAPP-A in trophoblast CM (n = 3) and did not change in the presence of IGF-II (1-100 ng/ml). Cultured human endometrial stromal cells (n = 4) secreted low levels of PAPP-A (6.25 +/- 3.6 mIU/liter.10(5) cells). A physiological inhibitor of PAPP-A, the proform of eosinophil major basic protein (proMBP), was detected in trophoblast CM at levels of 1853 +/- 308 mIU/liter.10(5) cells, determined by specific ELISA, and was nearly undetectable in CM of human endometrial stromal cells. Upon in vitro decidualization of endometrial stromal cells with progesterone, PAPP-A levels in CM increased nearly 9-fold without a concomitant change in proMBP. In contrast to the experiments with trophoblasts, IGF-II and the IGF analogues, Leu(27) IGF-II, and Des (1-6) IGF-II, resulted in a dose-dependent decrease of PAPP-A levels in decidualized endometrial stromal CM by 70-90%, and a dose-dependent increase in proMBP of 14- to 41-fold. The data demonstrate conclusively that the IGF-II-dependent

IGFBP-4 protease of human trophoblast and decidual origin is PAPP-A.
Furthermore, the differential regulation of decidual PAPP-A and proMBP by
insulin-like peptides supports a role for trophoblast-derived IGF-II as a
paracrine regulator of these maternal decidual products that have the
potential to regulate IGF-II bioavailability at the trophoblast-decidual
interface. Overall, the data underscore potential roles for a complex
family of enzyme (PAPP-A), substrate (IGFBP-4), inhibitor (proMBP), and
cofactor (IGF-II) in the placental bed during human implantation.

L3 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights
reserved on STN DUPLICATE 4
AN 2001166450 EMBASE
TI Pregnancy-associated plasma protein-A is the insulin-like growth factor
binding protein-4 protease secreted by human ovarian granulosa cells and
is a marker of dominant follicle selection and the corpus luteum.
AU Conover C.A.; Faessen G.F.; Ilg K.E.; Chandrasekher Y.A.; Christiansen M.;
Overgaard M.T.; Oxvig C.; Giudice L.C.
CS Dr. L.C. Giudice, Dept GYN, Stanford University Medical Center, Stanford,
CA 94305, United States
SO Endocrinology, (2001) Vol. 142, No. 5, pp. 2155-2158.
Refs: 24
ISSN: 0013-7227 CODEN: ENDOAO
CY United States
DT Journal; Article
FS 003 Endocrinology
010 Obstetrics and Gynecology
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 20010523
Last Updated on STN: 20010523
AB Insulin-like growth factors (IGFs), IGF binding proteins (IGFBPs), and
IGFBP proteases are important in ovarian function. IGFs stimulate
granulosa steroidogenesis, an effect that is inhibited by IGFBP-4 and
augmented by IGFBP-4 proteolysis. We have recently identified the IGFBP-4

protease in human ovarian follicular fluid (FF) as pregnancy-associated plasma protein-A (PAPP-A). In the current study, we identify the IGFBP-4 protease secreted by cultured human ovarian granulosa cells as PAPP-A, based on specific immunoinhibition and immunodepletion of the **IGFBP-4 protease** activity with PAPP-A **polyclonal antibodies** and immunorecognition by PAPP-A monoclonal antibodies in ELISA. PAPP-A was barely detectable in conditioned media (CM) from granulosa derived from ≤ 9 mm androgendominant follicles, but was secreted by cultured granulosa from estrogen-dominant follicles ≥ 9 mm, coincident with dominant follicle selection, and by luteinizing granulosa. PAPP-A levels in CM from the latter did not change in response to IGF-II or hCG (100 ng/mL). A naturally occurring inhibitor of PAPP-A, proform of eosinophil major basic protein (proMBP), was detected by ELISA in estrogen-dominant follicular fluid FF, but not in CM from granulosa or luteinizing granulosa cells treated with IGF-II (0-200 ng/mL), FSH (0-100 ng/mL) or hCG (0-100 ng/mL), suggesting an alternative source (other than granulosa) for proMBP, compared to PAPP-A. The data demonstrate granulosa cells as a source of PAPP-A in human ovary and suggest that PAPP-A is a marker of ovarian follicle selection and corpus luteum formation. In addition the data suggest complex regulation of this system in human ovary.

L3 ANSWER 5 OF 8 MEDLINE on STN
AN 2001262826 MEDLINE
DN PubMed ID: 11316785
TI Pregnancy-associated plasma protein-a is the insulin-like growth factor binding protein-4 protease secreted by human ovarian granulosa cells and is a marker of dominant follicle selection and the corpus luteum.
AU Conover C A; Faessen G F; Ilg K E; Chandrasekher Y A; Christiansen M; Overgaard M T; Oxvig C; Giudice L C
CS Endocrine Unit, Mayo Clinic, Rochester, Minnesota 55905, USA.
NC HD31579-07 (NICHD)
SO Endocrinology, (2001 May) 142 (5) 2155.
Journal code: 0375040. ISSN: 0013-7227.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
AB Insulin-like growth factors (IGFs), IGF binding proteins (IGFBPs), and
IGFBP proteases are important in ovarian function. IGFs stimulate
granulosa steroidogenesis, an effect that is inhibited by IGFBP-4 and
augmented by IGFBP-4 proteolysis. We have recently identified the IGFBP-4
protease in human ovarian follicular fluid (FF) as pregnancy-associated
plasma protein-A (PAPP-A). In the current study, we identify the IGFBP-4
protease secreted by cultured human ovarian granulosa cells as PAPP-A,
based on specific immunoinhibition and immunodepletion of the
IGFBP-4 protease activity with PAPP-A
polyclonal antibodies and immunorecognition by PAPP-A
monoclonal antibodies in ELISA. PAPP-A was barely detectable in
conditioned media (CM) from granulosa derived from </=9 mm
androgen-dominant follicles, but was secreted by cultured granulosa from
estrogen-dominant follicles >/=9 mm, coincident with dominant follicle
selection, and by luteinizing granulosa. PAPP-A levels in CM from the
latter did not change in response to IGF-II or hCG (100 ng/mL). A
naturally occurring inhibitor of PAPP-A, proform of eosinophil major basic
protein (proMBP), was detected by ELISA in estrogen-dominant follicular
fluid FF, but not in CM from granulosa or luteinizing granulosa cells
treated with IGF-II (0-200 ng/mL), FSH (0-100 ng/mL) or hCG (0-100 ng/mL),
suggesting an alternative source (other than granulosa) for proMBP,
compared to PAPP-A. The data demonstrate granulosa cells as a source of
PAPP-A in human ovary and suggest that PAPP-A is a marker of ovarian
follicle selection and corpus luteum formation. In addition the data
suggest complex regulation of this system in human ovary.

L3 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 5
AN 2001260195 MEDLINE
DN PubMed ID: 11231911
TI Insulin-like growth factor binding protein-4 protease produced by smooth
muscle cells increases in the coronary artery after angioplasty.
AU Bayes-Genis A; Schwartz R S; Lewis D A; Overgaard M T; Christiansen M;
Oxvig C; Ashai K; Holmes D R Jr; Conover C A
CS Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, Minnesota, USA.
SO Arteriosclerosis, thrombosis, and vascular biology, (2001 Mar) 21 (3)
335-41.
Journal code: 9505803. ISSN: 1524-4636.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
AB Insulin-like growth factor (IGF)-I stimulates vascular smooth muscle cell
(VSMC) migration and proliferation, which are fundamental to neointimal
hyperplasia in postangioplasty restenosis. IGF-I action is modulated by
several high-affinity IGF binding proteins (IGFBPs). IGFBP-4 is the
predominant IGFBP produced by VSMCs and is a potent inhibitor of IGF-I
action. However, specific IGFBP-4 proteases can cleave IGFBP-4 and
liberate active IGF-I. In this study, we document IGFBP-4 protease
produced by human and porcine coronary artery VSMCs in culture as
pregnancy-associated plasma protein-A (PAPP-A). This was shown by a
distinctive IGFBP-4 cleavage pattern, specific inhibition of IGFBP
-**4 protease** activity with PAPP-A **polyclonal antibodies**, and immunorecognition of PAPP-A by monoclonal
antibodies. Furthermore, we found a 2-fold increase in IGFBP-4 protease
activity in injured porcine VSMC cultures in vitro ($P<0.05$). We also
evaluated IGFBP-4 protease/PAPP-A expression in vivo after coronary artery
balloon injury. Twenty-five immature female pigs underwent coronary

overstretch balloon injury, and vessels were examined at defined time points after the procedure. Abundant PAPP-A expression was observed in the cytoplasm of medial and neointimal cells 7, 14, and 28 days after angioplasty (P<0.01 vs control). The highest PAPP-A labeling indices were located in the neointima (36.1+/-2.1%) and the media (31.7+/-1.2%) 28 days after injury. Western blot analysis confirmed increased PAPP-A in injured vessels. PAPP-A, a regulator of IGF-I bioavailability through proteolysis of IGFBP-4, is thus expressed by VSMCs in vitro and in restenotic lesions in vivo. These results suggest a possible role for PAPP-A in neointimal hyperplasia.

L3 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 6
AN 2000066728 MEDLINE
DN PubMed ID: 10599745
TI Evidence that the insulin-like growth factor binding protein-4 protease in human ovarian follicular fluid is pregnancy associated plasma protein-A.
AU Conover C A; Oxvig C; Overgaard M T; Christiansen M; Giudice L C
CS Endocrine Research Unit, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.. Conover.Cheryl@Mayo.Edu
NC HD 31579-05 (NICHD)
SO Journal of clinical endocrinology and metabolism, (1999 Dec) 84 (12) 4742-5.
Journal code: 0375362. ISSN: 0021-972X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200001
ED Entered STN: 20000124
Last Updated on STN: 20000124
Entered Medline: 20000107
AB Ovarian insulin-like growth factor binding protein-4 (IGFBP-4) proteolysis is involved in the regulation of follicular development, but until now the identity of the responsible enzyme was unknown. In this study, we identify the IGFBP4 protease in human follicular fluid as pregnancy

associated plasma protein-A (PAPP-A) based on distinctive IGFBP-4 cleavage
pattern, the same protease inhibitor profile, specific inhibition and
immunodepletion of **IGFBP-4 protease** activity
with PAPP-A **polyclonal antibodies**, and
immunorecognition by PAPP-A monoclonal antibodies in ELISA. Furthermore,
PAPP-A levels in estrogen-dominant and androgen-dominant follicular fluids
reflect their IGFBP-4 proteolytic activity. PAPP-A was also secreted by
human granulosa cells, the reputed source of IGFBP-4 protease activity in
follicular fluid. We have the molecular and biochemical tools to begin to
delineate the regulation and biological function of PAPP-A in normal and
dysregulated follicular development and atresia.

L3 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 7
AN 1999179030 MEDLINE
DN PubMed ID: 10077652
TI The insulin-like growth factor (IGF)-dependent IGF binding protein-4
protease secreted by human fibroblasts is pregnancy-associated plasma
protein-A.
AU Lawrence J B; Oxvig C; Overgaard M T; Sottrup-Jensen L; Gleich G J; Hays L
G; Yates J R 3rd; Conover C A
CS Endocrine Research Unit, Mayo Clinic and Mayo Foundation, Rochester, MN
55905, USA.
NC AI09728 (NIAID)
DK07352 (NIDDK)
GM52095 (NIGMS)
SO Proceedings of the National Academy of Sciences of the United States of
America, (1999 Mar 16) 96 (6) 3149-53.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990601
Last Updated on STN: 20000303
Entered Medline: 19990520
AB Proteolytic cleavage of the six known insulin-like growth factor binding
proteins (IGFBPs) is a powerful means of rapid structure and function

modification of these important growth-regulatory proteins. Intact IGFBP-4 is a potent inhibitor of IGF action in vitro, and cleavage of IGFBP-4 has been shown to abolish its ability to inhibit IGF stimulatory effects in a variety of systems, suggesting that IGFBP-4 proteolysis acts as a positive regulator of IGF bioavailability. Here we report the isolation of an IGF-dependent IGFBP-4-specific protease from human fibroblast-conditioned media and its identification by mass spectrometry microsequencing as pregnancy-associated plasma protein-A (PAPP-A), a protein of unknown function found in high concentrations in the maternal circulation during pregnancy. **Antibodies** raised against PAPP-A both inhibited and immunodepleted **IGFBP-4 protease** activity in human fibroblast-conditioned media. Moreover, PAPP-A purified from pregnancy sera had IGF-dependent IGFBP-4 protease activity. PAPP-A mRNA was expressed by the human fibroblasts and osteoblasts, and PAPP-A protein was secreted into the culture medium. In conclusion, we have identified an IGF-dependent IGFBP protease and at the same time assigned a function to PAPP-A. This represents an unanticipated union of two areas of research that were not linked in any way before this report.

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Pregnancy-associated plasma protein-A proteolytic activity in rat vertebral cell cultures: stimulation by dexamethasone--a potential mechanism for glucocorticoid regulation of osteoprogenitor proliferation and differentiation.
J Cell Physiol. 2005 Sep;204(3):848-58.
PMID: 15754336 [PubMed - indexed for MEDLINE]

2: Qin QP, Kokkala S, Lund J, Tamm N, Voipio-Pulkki LM, Pettersson K. Related Articles, Links

Molecular distinction of circulating pregnancy-associated plasma protein A in myocardial infarction and pregnancy.
Clin Chem. 2005 Jan;51(1):75-83.
PMID: 15613709 [PubMed - indexed for MEDLINE]

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J Endocrinol. 2004 Sep;182(3):457-66.
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[Role of proteins of the macroglobulin family in the mechanisms of infection]
Zh Mikrobiol Epidemiol Immunobiol. 2004 May-Jun;(3):105-12. Review. Russian.
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Pregnancy-associated plasma protein-a production in rat granulosa cells: stimulation by follicle-stimulating hormone and inhibition by the oocyte-derived bone morphogenetic protein-15.
Endocrinology. 2004 Aug;145(8):3686-95. Epub 2004 Apr 15.
PMID: 15087430 [PubMed - indexed for MEDLINE]

6: Sivanandam AS, Mohan S, Kita H, Kapur S, Chen ST, Linkhart TA, Bagi G, Baylink DJ, Qin X. Related Articles, Links

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Biochem J. 2004 Apr 1;379(Pt 1):57-64.
PMID: 14705967 [PubMed - indexed for MEDLINE]

7: Christiansen M, Jaliashvili I. Related Articles, Links

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Scand J Clin Lab Invest. 2003;63(6):407-15.
PMID: 14594321 [PubMed - indexed for MEDLINE]

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